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EXAMINER	
SANDALS, WILLIAM O	

ART UNIT	PAPER NUMBER
1636	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/359,975	Weiner et al.
Examiner	**Art Unit**
William Sandals	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 3, 2002*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96, and 115-157* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96, and 115-157* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Arguments

1. Claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96 and 115-157 are pending.

2. A statement in Paper No. 17, filed December 3, 2002 has indicated the intention to file a terminal disclaimer in view of the Double Patenting rejection of claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96 and 115-157 over US 5,981,505, US 5,817,637 and US 5,593,972. At this time, no terminal disclaimer has been filed, so the rejection stands and is repeated below.

3. Arguments regarding the rejection of claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96 and 115-157 under Double Patenting over US 5,739,118 have been considered and are found convincing. The rejection of the claims over US 5,739,118 has been withdrawn.

4. Arguments filed in Paper No. 17 regarding the rejection of claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96 and 115-157 under 35 USC 112, first paragraph, have been fully considered but they are not persuasive. The response to the arguments is contained in the rejection repeated below.

5. Arguments filed in Paper No. 17 regarding the rejection of claims 115-118, 120 and 121 under 35 USC 102 have overcome the rejection, and the rejection is withdrawn.

6. Arguments filed in Paper No. 17 regarding the rejection of claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96 and 115-157 under 35 USC 103(a) have been fully considered but they are not persuasive. The response to the arguments is contained in the rejection repeated below.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 58, 59, 63, 64, 67-72, 75-76, 84-86, 94-96 and 115-157 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6-14, 18-56 and 69-75 of U.S. Patent No. 5,981,505. Although the conflicting claims

are not identical, they are not patentably distinct from each other because the claims of US 5,981,505 are drawn to a pharmaceutical composition comprising a DNA molecule and a polynucleotide function enhancer, a method of immunizing with the composition, and a method of introducing the composition to cells of a host. The instant claimed invention is drawn to a pharmaceutical composition comprising a DNA molecule and a polynucleotide function enhancer, a method of immunizing with the composition, and a method of introducing the composition to cells of a host.

9. Claims 58, 59, 63, 64 and 122-125 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-24 and 30-32 of U.S. Patent No. 5,817,637. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of US 5,817,637 are drawn to a pharmaceutical composition comprising a DNA molecule and a polynucleotide function enhancer. The instant claimed invention is drawn to a pharmaceutical composition comprising a DNA molecule and a polynucleotide function enhancer.

10. Claims 67-72, 75-76, 84-86, 94-96 and 115-121 and 126-157 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 14-17 of U.S. Patent No. 5,830,876. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of US 5,830,876 are

drawn to a method of immunizing with a composition comprising a DNA molecule and a polynucleotide function enhancer, and a method of introducing the composition to cells of a host. The instant claimed invention is drawn to a method of immunizing with a composition comprising a DNA molecule and a polynucleotide function enhancer, and a method of introducing the composition to cells of a host.

11. Claims 67-72, 75-76, 84-86, 94-96 and 115-121 and 126-157 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,593,972. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of US 5,593,972 are drawn to a method of immunizing with a composition comprising a DNA molecule and a polynucleotide function enhancer, and a method of introducing the composition to cells of a host. The instant claimed invention is drawn to a method of immunizing with a composition comprising a DNA molecule and a polynucleotide function enhancer, and a method of introducing the composition to cells of a host.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96 and 115-157 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a pharmaceutical composition comprising DNA and a polynucleotide function enhancer and methods of immunization with the composition. While applicants have shown a composition comprising DNA and a polynucleotide function enhancer, the only data presented are model systems which are not predictive of success in production of a pharmaceutical vaccine with a pharmaceutical composition comprising DNA and a polynucleotide function enhancer. The specification, while being enabling for the production of antibodies for non-therapeutic purposes, does not reasonably provide enablement for the therapeutic immunization of an animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to therapeutically immunize an animal with the invention commensurate in scope with these claims. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve demonstration that a composition comprising DNA and a polynucleotide

function enhancer provides an immune response. It is known that production of an immune response is dependent upon a particular antigenic presentation and appropriate adjuvant. The identity of a specific antigen and demonstration of the immunogenicity of the specific antigen is not predictable, since each potential antigen must be tested to determine if it will elicit an immune response. Weiner et al. (Scientific American, Vol. 281, 1999) at page 37, column 2, middle, state that human trials have been conducted to determine the safety of an HIV-1 vaccine, but that "[s]uch trials do not assess disease prevention". The article goes on to discuss the fact that reports of humoral and cellular immunity have been achieved and "[i]n common with traditional vaccines, though, current genetic approaches will probably have to be combined in many cases with generalized immune stimulators (adjuvants) in order to elicit the strong immune responses required to shield recipients from future infections". These teachings by Weiner et al. make clear that a great deal of experimentation is common to all vaccine production.

b- Only prophetic guidance and no examples are presented in the instant specification.

c- The nature of the invention is complex. The use of DNA for immunization and passive protection is a new and developing art as taught in Cho et al. at the abstract "[t]he factors essential for the successful development of this new claims of therapeutic agents are not necessarily the same as those for conventional small organic molecules" and at page 157, column 1 bottom, bridging to column 2, top "formidable transport and delivery problems are associated with macromolecular therapeutic agents. With all of these disadvantages, one might wonder why investigators remain so interested in the prospect of using macromolecules as drugs. The answer

lies in the potentially exquisite specificity that one can, at least theoretically, attain by using proteins or genes as therapeutic agents. The challenge is to convert the potentiality of macromolecular drugs into practical reality".

d- The prior art at the time of filing of the instant priority document Application No. 08/124,962, filed September 21, 1993, was teaching that it was unknown if DNA vaccines would be effective.

e- Those of skill in the art have taught the unpredictability of DNA vaccines. Rabinovich et al. taught at page 1401, column 3, "[t]he advent of recombinant DNA technology has stimulated the production and testing of new subunit vaccines designed to be safer and more efficient. Unfortunately, the limited immunogenicity of many of these candidates has hindered their development as potential vaccines. Strategies to enhance the immunogenicity of these candidate vaccines are therefore critical". Webster et al. taught at page 281 "[t]he ultimate vector for use in DNA immunization in humans and other animals, that will meet all of the above requirements, is clearly desirable, but has not yet been perfected. Plasmids for use in DNA immunization will continue to be refined in the coming years". Piscatelli et al. taught at page 68, column 2, bottom bridging to page 69, column 3, top, that those of skill in the art were still evaluating the use of DNA to produce an HIV immunization. Yasutomi et al. taught at the abstract that attempts to immunize monkeys with the SIV Gag protein antigen failed to produce immune protection, despite the fact that the attempt to immunize produced a strong cytotoxic T cell response. These teachings highlight the fact that the state of the art in vaccine production is still a trial and error

process, with little advance knowledge of which if any potential vaccine will have any effect. And as stated above, there can be no prediction of immune protection in an individual animal because the state of the vaccine art is largely dependent upon an empirical experimental approach.

f- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

Response to Arguments

14. Arguments set forth in Paper No. 9 assert that the instant invention is enabled because the production of an antibody is demonstration of immunization.

The production of an antibody should not be confused with a production of immunity. Antibody production in animals has been routine for decades, but producing immunity by vaccination is not at all routine, and immunization is still a trial and error process.

15. Arguments assert in Paper No. 9 that examples 3, 28, 29, and 30 are working examples of DNA pharmaceutical compositions that produce an effective immune response in a mouse.

These examples demonstrate that an immune response can be mounted against a peptide encoded by a viral sequence which has been transfected into cells and subsequently expressed on the surface of the cells. Peptides expressed on cells have been used as targets for animal models of cellular immunity and humoral immunity for at least a decade. This, once again, does not demonstrate that the animal has been immunized against a pathogen, and is not a recognized

animal model for immunity against a pathogen. Rabinovich et al. and Piscitelli et al. taught that the ability to produce an antibody in an animal by introduction of naked DNA was well known to those of skill in the art. The production of an antibody in an animal with naked DNA was not a demonstration of vaccination against a pathogen or a proliferative disorder.

16. Arguments assert in Paper No. 9 at Page 4, bottom bridging to the top of Page 5 that even though the instant specification fails to provide any working examples of the use a composition of DNA and bupivacaine as claimed in the instant invention, that one of ordinary skill in the art may use the teachings of the instant specification as guidance for the practice of the method.

This issue is problematic, since Danko et al. (Gene Therapy, Vol. 1(2):114-121, 1994, see especially figure 3) teaches away from the co-administration of bupivacaine and DNA. Danko et al. taught that bupivacaine was effective only when administered at least 3 days prior the administration of the DNA. Similarly, the instant specification teaches the administration of bupivacaine 24 hours in advance of the administration of DNA in working examples 3, 28 and 43. The instant specification provides only prophetic teaching of co-administration of bupivacaine and DNA at page 27, line 15 bridging to page 29, line 34.

17. Arguments set forth in Paper No. 9 assert that Cho et al. taught "optimization" of the production of vaccines as cited at page 156, column 2, lines 6-12.

With continued reading of the passage cited, Cho et al. goes on a lines 12-25 to emphasize the problems and some of the unknown factors which still face developers of the art.

In short, Cho et al. do not teach "optimization" at all, but rather, a careful reading of the entire article makes the point that immunization with DNA is a developing and poorly understood art.

18. Arguments set forth in Paper No. 9 assert that this examiner alleges that the field of DNA immunization is unpredictable in general, even today. It is further asserted that this position is lacks evidence.

While it is true that the field of DNA immunization is not well understood, even today, this examiner did not make that assertion in the repeated rejection above. But, for the record, Chattergoon et al., which is cited in Paper No. 9 as evidence that DNA technology is enabled, recites in the abstract "[e]xpression of these delivered genes has important immunological consequences and **may** (emphasis added) result in the specific immune activation of the host against the novel expressed antigens. The recent demonstration by laboratories that these immune responses are protective **in some infectious disease experimental models** (emphasis added) as well as cancers **is viewed with cautious optimism** (emphasis added)....this technology will dramatically influence the production of **a new generation of experimental vaccines and immune therapies**" (emphasis added). It should be noted that the words are prophetic, and do not in any way state that there is certainty as to the outcome of any immunization.

19. Arguments set forth in Paper No. 9 assert that the invention is not a vaccine, but a pharmaceutical composition and a method for immunizing an individual, and a method for introducing DNA into cells of an individual.

The only utility described in the instant specification for the instant claimed composition is the production of immunity to pathogens and proliferative disorders in an animal. Since this is the only utility described, the composition and methods have only one utility, namely, the production of immunity to pathogens and proliferative disorders in an animal by the introduction of a DNA into the cell of the animal (in other words, a vaccine). Therefore, the DNA composition is a vaccine.

20. Arguments set forth in Paper No. 9 cite Weiner et al. (Scientific American, 1999) as proof of the enablement of the DNA vaccine art. At pages 40-41 in the section entitled "Getting From Here To There".

Many of the enablement deficiencies cited in the rejection above are discussed along with the presentation of some inventive solutions to the problems of vaccination with DNA. The tenor of the article is summarized at page 41, columns 2-3 "[a]s the years go by, the inherent manipulability of DNA should make it a vehicle of choice for teasing apart the body's complex immune responses to different disease-causing agents. With such information in hand, vaccine makers should be able to design vaccines that will channel immune responses down selected pathways. In the past, manufacturers had no way to custom-tailor their products easily and inexpensively. In the future, such "rationally" designed genetic vaccines are likely to provide new immune therapies for cancer and powerful ways to prevent or minimize any number of devilish infections that elude human control today". This makes it eminently clear that today's

skilled artisan does not have the skill to predictably effect an immune response using a DNA vaccine.

21. Arguments set forth in Paper No. 9 assert that the passage cited in the above rejection addresses subunit vaccines, and that the instant invention is not drawn to subunit vaccines.

The passage from Rabinovich et al. taught **DNA** subunit vaccines. Examples 43-56 of the instant specification use naked DNA subunit constructs to produce an immune response in an animal. While the claims are not drawn to DNA subunit vaccines, examples 43-56 are presented in the specification as evidence of enablement of the instant invention. If the instant examples 43-56 do not pertain to the instant claimed invention, then it should be so stated. At such time as it is clear that DNA subunit vaccines are not being contemplated as claimed subject matter then the rejection will be so amended to reflect that position.

22. Arguments set forth in Paper No. 9 assert that Webster et al. taught the successful introduction of DNA into an animal and the successful production of an antibody to the expressed product of the introduced DNA in the animal.

Once again, the production of an antibody in an animal does not per se produce an immunity to a disease or disorder. The argument is therefore not found convincing.

23. Arguments set forth in Paper No. 9 assert that Piscitelli et al. taught the successful production of an antibody to an HIV protein in an animal.

Once again, the production of an antibody in an animal does not per se produce an immunity to a disease or disorder. The argument is therefore not found convincing.

24. It is further argued in Paper No. 9 that it is "very likely that humans can also be effectively immunized with AIDS antigens without undue experimentation".

Once again, the production of an antibody in an animal does not per se produce an immunity to a disease or disorder. As shown in the cited art of the above rejection, and repeated in the Chattergoon et al. and Weiner et al. references, the state of the art shows that one of skill in the art cannot make and use a DNA vaccine without a significant amount of non-routine experimentation. The argument is therefore not found convincing.

25. It is argued in Paper No. 9 that the Wands analysis of the above rejection is flawed because each factor has not been properly analyzed individually.

The argument is made that "undue experimentation" is the key to the argument of each section. The above analysis does indeed follow the Wands factors, as set forth in sections a) through f). Each factor is addressed with references which fully support the arguments. This fact is clearly made in the above responses to the arguments set forth in Paper No. 9. The key element of "undue experimentation" is the linchpin of enablement, and as such, has been emphasized in the rejection. Reference to "undue experimentation" in the rejection emphasizes the fact that "undue experimentation" is necessary to practice the claimed invention and is deemed to be an obvious, albeit reiterated point.

26. Paper No. 9, filed February 28, 2002 presents a rebuttal of the instant forgoing rejection at page 3, by suggesting that the general textbook by Harlow and Lane is proof that the field of immunology is well developed.

This is not a point at issue and as such is not considered relevant to the rejection based upon the general lack of enablement of the vaccine art.

27. Paper No. 9 asserts at pages 3-4 that production of antigenic proteins was enabled.

Once again, this is not a point at issue and is not considered relevant to the facts of the rejection.

28. Paper No. 9 asserts at pages 4-5 that examples presented in the specification demonstrate a DNA vaccine which was effective against tumors in a mouse.

As stated above, the examples of the mouse model system presented in the instant specification are not predictive of success of a vaccine against a pathogenic agent. Each of the recited teachings above make it abundantly clear that a successful vaccination method cannot be predicted, and must be proved by a trial and error process.

29. Paper No. 9, page 5, has challenged the language "delivery of DNA to an animal for immunization" in the previous rejection under 35 USC 112, first paragraph, stating that "delivery of DNA to an animal for immunization" is well-established and routine.

This language has been misconstrued in its meaning. Therefore the language has been changed to make the meaning more clear.

30. Paper No. 9, pages 6 and 7, asserts that the claimed invention is not a vaccine. It states that the claims are drawn to a method of immunizing an animal, or a method of introducing a DNA into the cells of an animal.

Claims 84 and 94, for example, recite a "protective immune response" or a "therapeutic immune response". These claims make clear that the method is involving the use of the DNA as a vaccine. The instant enablement rejection is directed to the lack of teachings in the prior art regarding support of enablement of making a vaccine. The issue of producing cellular or humoral immune responses by injection of a DNA, with or without a polynucleotide function enhancer, is dealt with in the instant rejection under 35 USC 103.

31. Paper No. 9, at pages 7-8 asserts that the teachings of Webster et al. teaches "that there are vectors successfully being used to generate an immune response against encoded proteins".

Webster et al. teach that immunity has been produced against influenza, rabies and hepatitis B. These specific successes are a result of the usual trial and error process that has been the hallmark of vaccine production. Webster et al. teaches in the conclusion at page 289, column 2, last paragraph, "[t]he mechanism of induction of immune responses in naive animals after DNA transfection is still largely unresolved". This is a definitive statement regarding the state of the art in 1997, which is fully four years past the priority date of the instant invention.

32. Paper No. 9, at pages 8-9 asserts that Piscatelli et al., at page 70, column 1 teach that an effective HIV DNA immunization already exists in animal models, and that it is "very likely that humans can also be effectively immunized with AIDS antigens without undue experimentation.

Piscatelli et al. teach at page 70, column 1-2 under the heading "Animal Models", that the HIV chimpanzee model is not predictive of success in humans. Piscatelli et al. states at page 70, column 2, bottom "[a]nimal models that assess safety and efficacy of vaccines cannot necessarily

predict the outcome of vaccination in humans; thus, candidate vaccines showing promise in animal experiments are undergoing clinical trials, including recombinant formulations of subunit derivatives, yeast-derived particles, and peptides. These trials are evaluating a broad spectrum of safety assessments and clinical, immunologic, and physiologic parameters following administration of the experimental vaccine". Piscatelli et al. make clear the trial and error process involved in vaccine production, and highlight the lack of predictability of the vaccine art.

33. Paper No. 13 asserts at page 6 that the references cited above have been mischaracterized.

To the contrary, the cited passages are to the point and represent the true state of the vaccine art. The above comments in items 1-31 attest to the accuracy of the rejection.

34. Paper No. 13 asserts that the invention is sufficiently described to allow those of skill in the art to practice the invention.

Once again, the state of the vaccine art is a trial and error process. This lack of general knowledge on predicting the outcome of a potential vaccine is the hallmark of the vaccine art. The model system used in the examples is not predictive of production of immune protection in an animal by a vaccine, as stated above.

35. Paper No. 13 asserts that there is no requirement for a complete understanding of a scientific field of endeavor to provide enablement.

In a situation where the scientific field of endeavor does not provide enabling teachings, the teachings of the specification must provide those teachings not available in the prior art. The specification does not provide those teachings, and is not enabled.

36. Paper No. 13 asserts that "an invention can be improved does not establish non-enablement".

Improvement is not an issue of the rejection.

37. Paper No. 13 asserts that the evidence of record demonstrates enablement of the invention.

The evidence of record has been evaluated above, including the newly submitted declaration by David Weiner. The evidence of record does not provide enablement as set forth above.

38. Paper No. 13 asserts that the underlying scientific bases remain not fully understood, but that this does not diminish the enablement under the patent law.

The teachings that are not provided in the prior art must be found in the teachings of the instant specification. The instant specification does not provide the necessary teachings as set forth above, and is not enabled.

39. Arguments set forth in Paper No. 17 assert at pages 3-4 that claims 148-157 are drawn to a method of inducing antibodies which is well within the ability of those skilled in the art and does not require undue experimentation.

Claim 148, from which claims 149-157 depend, recites at the last two lines "wherein said DNA molecule is taken up by cells in said tissue, said DNA sequence is expressed in said cells and an immune response is generated against said antigen". This makes it clear that claims 148-157 are drawn to a method of immunizing an animal, which is not enabled.

40. Arguments set forth in Paper No. 17 assert at page 5 that claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96 and 115-157 are enabled, that the amount of experimentation required to produce a vaccine is routine, and that the specification sets forth the teachings required to produce a protective immune response.

The prior art of record above sets forth in clear and unequivocal terms that making a vaccine is anything but routine. Making a vaccine is unpredictable. Each vaccine must be proven to work by a trial and error process. The experimentation required is therefore, not routine.

41. Arguments set forth in Paper No. 17 assert at page 5 that working examples are not required to enable the claimed invention.

As stated above in items 15 and 33, the lack of working examples, coupled with a lack of teachings in the prior art on how to practice the claimed invention shift the burden to the applicant to provide teachings in the instant specification. Since such teachings are not found in the instant specification, the claims are not enabled.

42. Arguments set forth in Paper No. 17 assert at pages 5-6 that 130 patents have been issued in the area of DNA vaccine technology. This is asserted to be proof of enablement.

Each patent is judged on its' own merits.

43. Arguments set forth in Paper No. 17 assert at page 5 that the declaration of David Weiner filed on February 28, 2002 shows that 1 out of 4 monkeys were protected by a DNA vaccine. It is asserted that this shows proof of enablement.

The declaration of David Weiner is insufficient to overcome the rejection. The reasons of record are in the non-final office action mailed on June 4, 2002. No evidence has been submitted to rebut the arguments of record. The declaration does not present evidence of proof of enablement. The protective immunization of 1 monkey out of 4 demonstrates the lack of predictability of the vaccine arts. Further, the protocol of the declaration does not appear to follow the teachings of the instant claims and specification, and the monkey which showed protection, apparently was not immunized according to the teachings of the instant claims and specification. An inspection of the data and the protocol of the declaration suggests that the only two monkeys which may have received DNA and the claimed polynucleotide function enhancer were in fact, not protected. Since the vaccine art is a trial and error process, and the since the declaration of David Weiner does not provide evidence to the contrary, the assertion of proof of enablement is not found convincing.

44. Arguments set forth in Paper No. 17 assert at page 6 that the production of antibodies is enabled as an alternate use.

The above rejection is directed to vaccines, vaccine production, and protective immunization. This argument is therefore moot.

Claim Rejections - 35 USC § 103

45. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

46. Claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96 and 115-157 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,214,804 (Felgner et al.) in view of Price et al. and WO 91/12329 (Booth et al.).

The claims are drawn to a pharmaceutical composition comprising a DNA encoding an intracellular pathogenic antigen and a polynucleotide function enhancer, and to a method of immunizing with a DNA molecule encoding a pathogenic antigen and a polynucleotide function enhancer, a method of introducing a DNA molecule and a polynucleotide function enhancer to cells of a host, and a method of inducing antibodies in an individual by introducing a DNA expression construct encoding an antigen and a polynucleotide function enhancer to immunize an individual.

Felgner et al. teach at the summary, column 13, line 12 to column 14, line 12, column 15, lines 18-36, column 21, lines 44-67, example 7 and the claims, a pharmaceutical composition comprising a DNA encoding an intracellular pathogenic antigen and a polynucleotide function enhancer, and to a method of introducing a DNA encoding a pathogenic antigen into an individual for production of an immune response, including the production of antibodies. The DNA encodes a viral antigen from an intracellular pathogen.

Felgner et al. did not teach that the method included the claimed polynucleotide function enhancer.

Booth et al. teach at the abstract and pages 6, 11, 16, 17, 21 and the claims, a method of introducing a retrovirus and a polynucleotide function enhancer to cells of a host. The site of introducing may be skeletal muscle. The viral vector encodes a viral antigen from an intracellular pathogen.

Price et al. teach at the materials and methods, a plasmid retroviral vector which encodes a foreign gene. The plasmid/retroviral vector is delivered to cells of an animal with a polynucleotide function enhancer where the foreign gene is expressed.

It would have been prima facie obvious to one of ordinary skill in the art at the time of filing the instant application to combine the teachings of Felgner et al. with Price et al. and Booth et al. because each of Felgner et al., Price et al. and Booth et al. teach the introduction of a vector encoding a foreign gene into cells of an animal to express the foreign gene in the animal. Price et al. make obvious the use of a DNA plasmid retroviral vector encoding a foreign gene in a method of delivering the vector into an animal with a polynucleotide function enhancer and expressing the foreign gene in the cells of an animal. Booth et al. make obvious the delivery of a retroviral vector encoding a pathogenic viral antigen with a polynucleotide function enhancer to express the viral antigen in an animal.

One of ordinary skill in the art would have been motivated to combine the teachings of Felgner et al. with Price et al. and Booth et al. because each of Felgner et al., Price et al. and Booth et al. teach the desirable and useful benefit of introducing a vector and a polynucleotide function enhancer to cells of a host, where the polynucleotide function enhancer increases the

uptake of the vector by the cells of the individual, thereby increasing the expression of the desired gene in the individual. Booth et al. teach the desirable and useful benefit of the instant claimed polynucleotide function enhancer. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Felgner et al., Price et al. and Booth et al.

Response to Arguments

47. Arguments set forth in Paper No. 17 assert at pages 7 and 9 that Booth et al. teach the use of a retroviral vector, which is RNA, not DNA.

This examiner thanks the applicant's representative for pointing out this obvious mistake and the language of the rejection has been corrected to reflect this fact.

48. Arguments set forth in Paper No. 17 assert at page 8 that Booth et al. teach away from the instant claimed invention, making it improper to combine the reference in the above rejection. Booth et al. is quoted "[t]he treatment of genetically-related diseases with techniques as DNA transfection has thus far, unfortunately, not met with great success." The argument at page 8 continues "[t]he specification goes on to describe the extreme limitations of using DNA techniques and does not discuss introducing DNA with a polynucleotide function enhancer". This is taken as teaching away.

Rather than teaching away, the Booth et al. reference simply provides a method for improving the delivery of a desired gene to a target cell in an animal, and is silent as to the use of the polynucleotide function enhancer in combination with DNA.

The above excerpt from Booth et al. is from the background section of the specification at page 7. The background section of Booth et al. teaches at page 9, lines 18-21 "[r]etroviral mediated gene transfer remains a relatively inefficient gene transfer system for adult tissues owing to low gene incorporation rates of target cells". Thus, the teachings in the background section of the specification of Booth et al. recite the deficiencies of both naked DNA transfection techniques and retroviral delivery to target cells. The method taught by Booth et al. is therefore an improvement of existing techniques of gene delivery. Booth et al. is silent about the use of a polynucleotide function enhancer with naked DNA, but in no way can be construed as a teaching away.

49. Arguments set forth in Paper No. 17 assert at page 9 that Booth et al. teaches RNA and Felgner et al. teach DNA, and thus there is no motivation to combine the references.

Felgner et al. teach at column 6, lines 38-49 that the nucleotide sequence may be either DNA or RNA. This makes clear the fact that Felgner et al. contemplated use of RNA in a method of delivery of a gene to a cell of an animal. The teachings of Booth et al. make clear the fact that the polynucleotide function enhancer is useful to increase expression of the desired gene in the target cells of the animal. Both Felgner et al. and Booth et al. teach the desirability of delivering the gene into muscle tissue, and they teach that the gene may be either a dystrophin gene or an viral pathogen antigen. Further, Felgner et al. teach at example 7, the use of a polynucleotide function enhancer (liposome) to facilitate expression of the desired gene in the target cell of the animal. The teachings of Felgner et al. and Booth et al. are therefore,

combinable, and the motivation to combine is provided by Booth et al., where Booth et al. teach the increased expression of the desired gene by use of the polynucleotide function enhancer.

Conclusion

50. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

a shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

51. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Thursday from 8:30 AM to 7:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Tech Center customer service center at telephone number (703) 308-0198.

William Sandals, Ph.D.
Examiner
February 21, 2003

John J. Doll, Director
Technology Center 1600

JAMES KETTER
PRIMARY EXAMINER